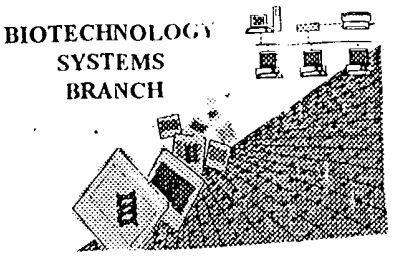

CRF Problem Report

The Biotechnology Systems Branch of the Scientific and Technical Information Center (STIC) experienced a problem when processing the following computer readable form (CRF):

Application Serial Number: 10/791,316
Filing Date: 3/1/04
Date Processed by STIC: 8/19/04

STIC Contact: **Mark Spencer: Telephone: 571-272-2510; Fax: 571-273-0221**

Nature of Problem:

The CRF (was):

____ (circle one) Damaged or Unreadable (for Unreadable, see attached)
____ Blank (no files on CRF) (see attached)
____ Empty file (filename present, but no bytes in file) (see attached)
____ Virus-infected. Virus name: _____ The STIC will not process the CRF.
____ Not saved in ASCII text
____ Sequence Listing was embedded in the file. According to Sequence Rules, submitted file should **only** be the Sequence Listing.
✓ Did not contain a Sequence Listing. (see attached sample)
____ Other:

PLEASE USE THE CHECKER VERSION 4.2 PROGRAM TO REDUCE ERRORS. SEE BELOW FOR ADDRESS:

http:/www.uspto.gov/web/offices/pac/checker/chkrnote.htm

Applicants submitting genetic sequence information electronically on diskette or CD-Rom should be aware that there is a possibility that the disk/CD-Rom may have been affected by treatment given to all incoming mail. Please consider using alternate methods of submission for the disk/CD-Rom or replacement disk/CD-Rom. Any reply including a sequence listing in electronic form should NOT be sent to the 20231 zip code address for the United States Patent and Trademark Office, and instead should be sent via the following to the indicated addresses:

1. EFS-Bio (<**http://www.uspto.gov/ebc/efs/downloads/documents.htm**> , **EFS Submission User Manual** - cPAVE)
2. **U.S. Postal Service**: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450
3. **Hand Carry, Federal Express, United Parcel Service, or other delivery service (EFFECTIVE 06/05/04):** U.S. Patent and Trademark Office, 220 20th Street S., Customer Window, Mail Stop Sequence, Crystal Plaza Two, Lobby, Room 1B03, Arlington, VA 22202

Revised 05/19/04

(Sample of submitted File)

10/791,316
IFW0

49870/CAB/R2682

SK3-1B TRANSGENIC MOUSE MODEL FOR SPINOCEREBELLAR ATAXIA AND HYPEREXCITABLE BEHAVIOR

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with Government support under Grant No. NIH MH59222, awarded by the National Institutes of Health. The Government may have certain rights in this invention.

INTRODUCTION

Small conductance calcium-activated potassium (SK) channels, products of the SK1-SK3 genes, are critical modulators of calcium signaling, firing frequency and inter-spike interval in the brain. The SK3 channel has been implicated in dominant ataxia, schizophrenia and anorexia nervosa. The SK3 gene and protein are described in U.S. Patent No. 6,165,719, the entire contents of which are incorporated by reference. Recently, we have described the isolation of a novel SK3 splice variant, SK3-1 B, which encodes a truncated product that suppresses SK channels in a dominant-negative manner (See Attachment 1). Such molecular suppression of endogenous SK channels in the brain should enhance neural excitability and induce calcium mediated excitotoxicty, analogous to the effect of the SK channel blocking neurotoxin apamin. To test this idea, we generated transgenic mice over-expressing SK3-1B in the brain under control of Thy1.2-SX, a neuron-specific promoter. Eleven transgenic founders have been identified and of these seven exhibit progressively worsening ataxia, intention tremor, and hyper-excitable behavior. The symptoms started at the 7th-8th week of life and progressively worsened.

Table 1 (Attachment 2) summarizes the clinical phenotype of all eleven founders. We analyzed the gait of transgenic (Tg) mice using ink imprints. Mice were allowed to walk on an inkpad and then onto a sheet of white paper. In contrast to control